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published in
Obesity Research
2005

DOI (link to publisher)
10.1038/oby.2005.221

document version
Publisher's PDF, also known as Version of record

Opposite Contributions of Trunk and Leg Fat Mass with Plasma Lipase Activities: The Hoorn Study

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Abstract

BOS, GRIËT, MARIEKE B. SNIJDER, GIEL NIJPELS, JACQUELINE M. DEKKER, COEN D.A. STEHOUWER, LEX M. BOUTER, ROBERT J. HEINE, AND HANS JANSEN. Opposite contributions of trunk and leg fat mass with plasma lipase activities: the Hoorn study. *Obes Res.* 2005;13:1817–1823.

Objective: Lipoprotein lipase (LPL) and hepatic lipase (HL) are essential in hydrolysis of triglyceride-rich lipoproteins. LPL activity is negatively, whereas HL activity is positively, associated with total body fat. We determined the associations of trunk and leg fat mass with plasma LPL and HL activities in a cross-sectional study.

Research Methods and Procedures: LPL and HL activities were determined in post-heparin plasma in a sample of 197 men and 209 women, 60 to 87 years of age. A total body DXA scan was performed to determine trunk and leg fat mass.

Results: In women, but not in men, trunk fat mass was negatively associated with LPL activity, whereas leg fat mass was positively associated, after mutual adjustment and adjustment for age. Standardized βs (95% confidence interval) for trunk and leg fat mass were −0.24 (−0.41; −0.08) and 0.14 (−0.02; 0.31), respectively (interaction by sex, $p = 0.03$). Larger trunk fat mass was associated with higher HL activity in men [0.48 (0.28; 0.68)] and women [0.40 (0.24; 0.56)]. A negative association of leg fat mass and HL activity was observed in men, although not statistically significant [−0.13 (−0.33; 0.06)], and in women [−0.28 (−0.38; −0.18)].

Discussion: Abdominal fat is associated with unfavorable and femoral fat with favorable LPL and HL activities in plasma.

Key words: lipase activity, intra-abdominal fat, femoral fat, DXA

Introduction

It is widely accepted that adiposity, in particular abdominal adiposity, is associated with insulin resistance and increased risk of type 2 diabetes (1–3).

It has been clearly shown that a preferential visceral accumulation of fat is independently related to insulin resistance (4). In contrast, larger femoral fat mass measured by DXA has been found to be associated with more favorable concentrations of lipid and glucose concentrations (5,6). Total body fat is associated with hepatic lipase (HL)[1] activity (7) but not with lipoprotein lipase (LPL) activity (8,9). LPL activity has been shown to be higher in femoral subcutaneous adipose fat than in visceral fat (10,11). The femoral region is, therefore, more likely to buffer circulating free fatty acids (FFAs) by promoting the uptake and the suppression of the lipolytic release into the circulation (12).

The primary functions of LPL include the clearance of triglyceride-rich chylomicrons and very-low-density lipoprotein particles from the bloodstream and the supply of FFAs to adipose tissue for storage and to skeletal muscle

Received for review March 16, 2004.
Accepted in final form July 25, 2005.
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[1] Nonstandard abbreviations: HL, hepatic lipase; LPL, lipoprotein lipase; FFA, free fatty acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OGTT, oral glucose tolerance test.

tissue for energy production. Whereas LPL is more closely related to triglyceride degradation for either energy (muscle) or storage (adipose tissue), HL plays a more important role in remodeling low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles by hydrolysis of triglycerides and phospholipids (13). HL activity is sensitive to sex hormones, with HL activity being lower in women than in men. Lower LPL activity and higher HL activity have been described in subjects with type 2 diabetes (14,15).

This study was designed to understand the relationship of body fat distribution, i.e., abdominal and femoral fat, with LPL and HL activities. The purpose of the study was to determine whether the associations of trunk fat and leg fat as measured by DXA with plasma LPL and HL activities are different.

Research Methods and Procedures

Design and Population

The Hoorn Study is a population-based cohort study of glucose metabolism and cardiovascular risk factors among the inhabitants of the municipality of Hoorn. The study started in 1989 and consisted of 2484 subjects, as described before (16). In 2000 to 2001, a follow-up was conducted in selected subjects 60 to 87 years of age. We invited all surviving subjects with type 2 diabetes ($n = 176$) and took random samples of individuals with normal glucose metabolism ($n = 705$) or impaired glucose metabolism ($n = 193$) based on their glucose metabolism status at the previous examination in 1996 to 1998 (1). Of the 1074 individuals invited for the 2000 to 2001 follow-up examination, 648 subjects participated (60.3%). Among the reasons for not participating in the follow-up examinations were lack of interest (30%), comorbidity (23%), high age (7%), unwillingness to travel (6%), participation considered too time-consuming (6%), and miscellaneous reasons (15%). Thirteen percent were complete non-responders. For this study, cross-sectional data of this 2000 to 2001 follow-up examination were examined. A sample of 585 participants was invited for the post-heparin test, of which 566 participated. The study was approved by the Ethical Review Committee of the Vrije Universiteit Medical Center. Informed consent was obtained from all participants.

Post-heparin Plasma Lipase Activity

LPL and HL activities were measured using an immunochemical method, as described previously (17), in plasma collected 20 minutes after contralateral intravenous administration of 50 IU/kg body weight heparin (Leo Pharmaceutical Products, Weesp, The Netherlands). One hundred seven samples were excluded from the analysis because of very low activities for LPL and HL in post-heparin plasma. Activities were considered very low if both LPL activity was <50 U/liter and HL activity was <72 U/liter. The post-heparin test was repeated in a sample of subjects with both low LPL and HL activities ($n = 10$), and normal activities were measured, indicating that insufficient heparin delivery was the cause of the low activity.

Genotyping HL Polymorphisms

DNA was extracted from frozen blood. We used the polymerase chain reaction method as described by Berk-Planken et al. (14) to assess the presence of the C>T variance in the hepatic lipase gene promoter.

Body Fat and Anthropometry

Body fat was measured by DXA (QDR-2000; Hologic Europe NV, Belgium). A total body fan beam DXA scan was performed to determine soft tissue composition at the standard regions of interest, i.e., trunk and legs. The software provided the lean mass, fat mass, and bone mineral mass for the total body and for the standard regions. In the analyses, we used fat mass in the trunk and in the legs. Weight and height were measured in barefoot subjects wearing light clothes. BMI was calculated by weight divided by height squared. Waist girth was measured at the level midway between the lowest rib margin and the iliac crest, and the hip girth was measured at the widest level over the greater trochanters. Waist to hip ratio was calculated by waist girth divided by hip girth.

Glycemic Control and Lipids

All participants underwent a 75-gram oral glucose tolerance test (OGTT), except those with previously diagnosed diabetes who were being treated with oral glucose-lowering medication or insulin. Fasting glucose and 2-hour postload glucose after OGTT were measured in plasma with the hexokinase method (Roche Diagnostics, Mannheim, Germany). Hemoglobin A_{1c} was analyzed by high-performance liquid chromatography (reference range, 4.3% to 6.1%). Fasting plasma glucose concentration and 2-hour postload plasma glucose concentration, total cholesterol, HDL-cholesterol, and triglycerides were measured by enzymatic methods (Roche Diagnostics). LDL-cholesterol was directly determined by the N-geneous assay (Genzyme, Cambridge, MA). FFAs were measured in plasma samples by the enzymatic colorimetric method (Wako Chemicals, Neuss, Germany). Insulin was determined using a two-site immunoradiometric test. Paired monoclonal antibodies were used (Medgenix Diagnostics, Fleurus, Belgium). This test is insulin specific and does not show cross-reactivity with proinsulin and split products.

Statistical Analysis

Three glucose metabolism categories were defined according to the WHO-99 criteria (18). Participants already known to have diabetes ($n = 51$) were excluded because treatment could influence the relationships under consider-

Table 1. Characteristics (means ± SD) of the study population stratified for sex and tertiles of trunk fat ($n = 406$)

	Tertiles of trunk fat					
	Men			Women		
	I	II	III	I	II	III
N	65	66	66	69	70	70
Age (years)	68 ± 6	70 ± 6	69 ± 6	69 ± 6	70 ± 6	70 ± 6
NGM, IGM, DM (%)	74/17/9	55/39/6	36/42/21	74/17/9	51/36/13	41/40/19
Fasting glucose (mM)	5.71 ± 0.65	5.80 ± 0.59	6.25 ± 0.98	5.55 ± 0.62	5.81 ± 0.77	6.13 ± 0.95
Postload glucose (mM)	5.92 ± 1.95	6.60 ± 2.33	7.65 ± 2.45	6.29 ± 2.18	7.29 ± 2.16	7.85 ± 2.31
Hemoglobin A_{1c} (%)	5.8 ± 0.5	5.8 ± 0.5	5.9 ± 0.6	5.8 ± 0.4	5.9 ± 0.5	6.0 ± 0.6
Insulin (pM)*	44 (30–58)	49 (37–66)	66 (46–88)	39 (32–51)	51 (39–75)	77 (57–104)
LPL activity (U/liter)	134 ± 46	127 ± 41	135 ± 39	167 ± 51	160 ± 55	149 ± 54
HL activity (U/liter)	370 ± 132	392 ± 130	473 ± 135	312 ± 111	329 ± 124	360 ± 117
CC/CT/TT (%)†	56/40/4	78/20/2	63/33/4	69/29/2	66/30/4	55/41/4
Total cholesterol (mM)	5.2 ± 1.0	5.5 ± 0.9	5.5 ± 1.0	6.2 ± 1.0	6.2 ± 0.9	6.1 ± 0.9
HDL-cholesterol (mM)	1.34 ± 0.43	1.26 ± 0.29	1.23 ± 0.32	1.70 ± 0.42	1.60 ± 0.43	1.53 ± 0.37
LDL-cholesterol (mM)	3.4 ± 0.8	3.6 ± 1.0	3.7 ± 0.9	3.9 ± 0.9	3.8 ± 0.8	3.9 ± 0.9
Triglycerides (mM)*	1.0 (0.9–1.4)	1.3 (1.0–1.9)	1.4 (1.1–2.0)	1.0 (0.8–1.5)	1.3 (0.9–1.8)	1.4 (1.1–1.9)
Lipid-lowering drugs (%)	12	20	17	10	14	14
β-blockers (%)	9	8	20	4	20	28
BMI (kg/m^2)	24.0 ± 1.8	26.2 ± 1.8	29.7 ± 3.0	23.8 ± 1.8	26.6 ± 2.0	31.3 ± 3.7
Waist-to-hip ratio	0.92 ± 0.05	0.97 ± 0.05	1.02 ± 0.05	0.82 ± 0.06	0.88 ± 0.06	0.90 ± 0.08
DXA total body fat (%)	21.0 ± 3.9	26.8 ± 3.0	33.6 ± 4.7	35.1 ± 4.6	41.3 ± 3.7	47.1 ± 4.2
Trunk fat (kg)	7.14 ± 2.07	11.17 ± 1.01	17.76 ± 4.74	9.02 ± 1.94	13.67 ± 1.50	20.23 ± 3.70
Leg fat (kg)	4.94 ± 1.24	6.13 ± 1.37	8.11 ± 2.14	8.73 ± 2.06	10.15 ± 2.66	12.85 ± 4.07

NGM, normal glucose metabolism; IGM, impaired glucose metabolism; DM, type 2 diabetes; LPL, lipoprotein lipase; HL, hepatic lipase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

* For insulin and triglyceride concentrations (skewed data), the median and interquartile ranges are shown.

† HL −480C/T polymorphism.

ation. Two subjects were excluded because of missing DXA data (logistical reasons). Thus, the study population consisted of 406 individuals: 197 men and 209 women.

Characteristics of the study population are presented by sex and tertiles of trunk fat. To visualize the associations of trunk and leg fat with LPL and HL activities, sex-specific tertiles of trunk fat and leg fat were created, and the population of each sex was divided into nine groups by creating a 3 × 3 table according to these tertiles. Age-adjusted LPL and HL activities were calculated in each group and shown in a figure. To study the independent associations of fat mass in the trunk and in the legs to the LPL and HL activities, multiple linear regression analyses were performed. LPL and HL activities were modeled as the dependent variables, and regional fat masses were entered as independent variables. All regression models were adjusted for age and lean mass and, subsequently, for triglycerides, insulin concentration, and FFAs. We tested for interactions of sex or glucose metabolism by calculating the *p* values of the respective interaction terms. All associations of the regression analyses are reported as standardized β. A standardized β of −0.1 indicates that, if the independent variable increases 1 SD, the dependent variable decreases 0.1 SD. Spearman correlation coefficients were calculated to evaluate relationships between variables. *p* values <0.05 (two-tailed) were considered statistically significant. Statistical analyses were performed with SPSS for Windows version 10.1.

Results

Table 1 shows the characteristics of men and women for tertiles of trunk fat. Figures 1 and 2 show mean LPL and HL

Figure 1: Age-adjusted means of plasma LPL activity according to tertiles of trunk fat and leg fat mass.

activities, adjusted for age, by combined tertiles of trunk fat and leg fat. In women, but not in men, LPL decreased over tertiles of trunk fat but increased over tertiles of leg fat. HL activity increased over tertiles of trunk fat, independently of leg fat mass, in both men and women. Additional adjustment for lean mass did not change the results (data not shown). It should be noted that, particularly in men, the number of subjects in the extreme groups was very small. The group with low trunk fat and high leg fat consisted of three men, and the group with high trunk fat and low leg fat contained only one person.

Using linear regression, neither trunk fat nor leg fat was significantly associated with LPL activity in men. In contrast, in women, trunk fat mass was significantly negatively associated with LPL activity, whereas leg fat was positively, although of borderline significance, associated with LPL activity (Table 2). The differences between men and women were statistically significant (interaction, $p = 0.03$). After adjustment for triglyceride or insulin concentrations, the association of trunk fat and LPL activity in women disappeared. For HL activity, in both men and women, trunk fat

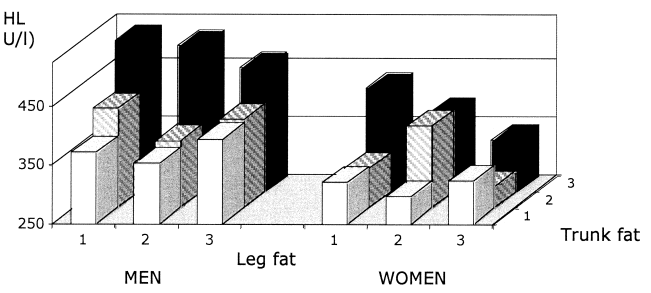

Figure 2: Age-adjusted means of plasma HL activity according to tertiles of leg fat and trunk fat mass. Tertiles of leg fat are now indicated on the *x*-axis and tertiles of trunk fat on the *z*-axis, in contrast to Figure 1.

was positively associated with HL. In women, and less strongly in men, leg fat was negatively associated (interaction by sex, $p = 0.10$). These associations were independent of triglyceride, insulin, and FFA concentrations. The associations did not clearly differ among subjects with normal glucose metabolism, impaired glucose metabolism, or diabetes.

Table 3 shows the associations of trunk and leg fat with LPL and HL activities, stratified for the HL −480 polymorphism. In subjects with −480 CT/TT, the association between fat masses and lipase activities was stronger than in the −480 CC group in men as well as women, although a test for interaction did not reach statistical significance.

Discussion

The main finding of this study is that in women, but not in men, larger trunk fat mass was associated with lower LPL activity in plasma, whereas larger leg fat mass was associated with higher LPL activity. Furthermore, trunk fat and HL activity were positively associated in men and in women. A negative association between leg fat mass and HL activity was observed, which was stronger in women than in men.

Several studies have investigated visceral fat in relation to LPL and HL activities. Greater abdominal fat and greater visceral fat have been found to be related to higher HL activity (19–22). Abdominal and visceral fat have been negatively associated with LPL activity in most (13,23), but not all, studies (8,24).

The design of our study cannot address the mechanism by which trunk fat and leg fat affect LPL and HL activities. It has been reported that high glucose increases HL mRNA levels, providing a molecular foundation for a role of hyperglycemia in altered lipoprotein metabolism (25). Previous studies have reported that insulin up-regulates the activity of HL through insulin-responsive elements in the HL promoter, suggesting that variants in this promoter may affect the ability of insulin to stimulate HL activity (26). Jansen et al. (27) reported an association between the HL promoter variants and insulin resistance, suggesting some potential mechanisms compatible with our results. When these HL genotypes (CC and CT/TT) were studied separately, the association was stronger in the CT/TT group, although a test for interaction did not reach statistical significance (Table 3). This suggests that the HL variant modulates the effect of fat mass on HL expression. This could be an important topic for further research because gene–lifestyle interactions may help to explain different outcomes of plasma lipoprotein response in relation to body fat, as well as conflicting results with regard to lipase activity and cardiovascular risk.

For LPL, it has been suggested that, compared with visceral fat, the subcutaneous femoral region is more effective in storing FFAs and thereby protecting other organs,

Table 2. Associations for trunk and leg fat mass with LPL and HL activities in men (n = 197) and women (n = 209)

			Standardized β (95% confidence interval)	
			Men	**Women**
LPL	Model 1	Trunk fat (kg)	0.01 (−0.21; 0.23)	−0.24 (−0.41; −0.08)
	Model 1 + triglycerides		0.12 (−0.11; 0.35)	−0.15 (−0.33; 0.03)
	Model 1 + insulin		0.05 (−0.18; 0.28)	−0.09 (−0.28; 0.10)
	Model 1 + FFAs		−0.02 (−0.24; 0.21)	−0.22 (−0.39; −0.04)
	Model 1	Leg fat (kg)	−0.05 (−0.27; 0.18)	0.14 (−0.02; 0.31)
	Model 1 + triglycerides		−0.11 (−0.33; 0.12)	0.06 (−0.11; 0.23)
	Model 1 + insulin		−0.04 (−0.26; 0.19)	0.10 (−0.06; 0.26)
	Model 1 + FFAs		0.01 (−0.22; 0.24)	0.14 (−0.02; 0.31)
HL	Model 1	Trunk fat (kg)	0.45 (0.25; 0.65)	0.40 (0.24; 0.56)
	Model 1 + triglycerides		0.43 (0.22; 0.65)	0.30 (0.13; 0.47)
	Model 1 + insulin		0.43 (0.22; 0.64)	0.33 (0.13; 0.52)
	Model 1 + FFAs		0.42 (0.21; 0.63)	0.40 (0.23; 0.57)
	Model 1	Leg fat (kg)	−0.09 (−0.29; 0.11)	−0.28 (−0.38; −0.18)
	Model 1 + triglycerides		−0.08 (−0.29; 0.12)	−0.19 (−0.30; −0.08)
	Model 1 + insulin		−0.08 (−0.29; 0.12)	−0.26 (−0.37; −0.16)
	Model 1 + FFAs		−0.06 (−0.27; 0.16)	−0.29 (−0.39; −0.18)

Model 1 adjusted for age and lean mass.

such as the liver, skeletal muscle tissue, and pancreas, from high FFA exposure, and in this way protects against the development of insulin resistance and/or ectopic accumulation of triglycerides (10,11,28). Our data support the hypothesis that this protective function is exerted through high LPL activity in women, because we observed a positive association between leg fat and LPL activity in women but not in men. The differences between men and women may be caused by the difference in the amount of leg fat (6 kg in men vs. 20 kg in women), suggesting a possible threshold. A limitation of our study is that plasma LPL activity consisted of LPL derived from all tissues, and no information on tissue-specific activity was available. In addition, DXA does not allow separate quantification of visceral fat and subcutaneous fat in the trunk. Therefore, it is not possible to study site-specific LPL activity or its relation to fat cell size (29) or the specific contributions of visceral fat or subcutaneous fat to the observed associations with trunk fat.

Unfortunately, ~20% of the lipase samples had to be excluded because of insufficient heparin delivery. The majority of excluded samples were among subjects with im-

Table 3. Associations for trunk and leg fat mass with HL activities in men and women stratified for HL polymorphism and adjusted for age and lean mass (n = 393)

		Standardized β (95% confidence interval)		
		CC (n = 258)	**CT/TT (n = 135)**	**p for interaction**
Men	Trunk fat (kg)	0.40 (0.15; 0.65)	0.52 (0.16; 0.88)	0.73
	Leg fat (kg)	−0.02 (−0.27; 0.23)	−0.21 (−0.59; 0.18)	0.36
Women	Trunk fat (kg)	0.27 (0.06; 0.48)	0.70 (0.43; 0.97)	0.29
	Leg fat (kg)	−0.16 (−0.35; 0.04)	−0.54 (−0.83; −0.26)	0.44

Table 4. Spearman correlations with LPL and HL activities

	LPL activity		HL activity	
	Men	**Women**	**Men**	**Women**
Age	−0.14 (0.05)	−0.16 (0.03)	−0.22 (0.002)	−0.04 (0.55)
HDL-cholesterol	0.24 (0.001)	0.40 (0.001)	−0.19 (0.008)	−0.15 (0.04)
Triglyceride	−0.08 (0.25)	−0.35 (<0.001)	0.22 (0.002)	0.13 (0.06)
Insulin	−0.09 (0.20)	−0.22 (<0.001)	0.21 (0.003)	0.28 (<0.001)
Total body fat (%)	−0.06 (0.39)	−0.07 (0.32)	0.26 (<0.001)	0.14 (0.04)

Values are Spearman's *R* (*p* value). HDL, high-density lipoprotein cholesterol.

paired glucose metabolism and type 2 diabetes. However, there were no noticeable differences between individuals who were excluded and the rest of the subjects with respect to lipoproteins, BMI, trunk fat, and leg fat (data not shown). Furthermore, LPL and HL activities showed the known associations (30,31) with age, sex, HDL-cholesterol, and triglyceride concentrations (Table 4). Moreover, after re-measurement of the post-heparin test in a sample of subjects with both low LPL and HL activities, normal LPL and HL activities were measured in these subjects.

Because of the cross-sectional design of this study, it is not possible to draw conclusions about cause or effect of the observed associations. Lipases might play a role in fat distribution, but fat distribution might influence plasma lipase activities, leading to a more-or-less atherogenic lipid profile. Thus, prospective studies are needed to determine the direction of the mechanisms.

In this study we showed in women, but not in men, that a larger trunk fat mass was associated with lower LPL activity, whereas a larger fat mass in the legs was positively associated with higher LPL activity. After adjustment for triglyceride or insulin concentration, these associations disappeared, possibly suggesting that lipid metabolism and insulin sensitivity are involved in differential stimulation of LPL by adipose tissue in different regions or that LPL activity is involved in the development of insulin resistance. We observed that larger trunk fat was associated with higher HL activity in men and women. An opposite association of leg fat and HL activity was observed in women but the association was not significant in men. Adjustment for triglyceride, insulin, and FFA concentrations did not alter these associations. In conclusion, the fat masses in the trunk and in the legs have an opposite association with plasma LPL and HL activities in women. In men, we observed an opposite association of trunk and leg fat mass with HL, but there were no associations of trunk or leg fat with LPL activity. Femoral fat might possibly protect against insulin resistance through more favorable LPL and HL activities.

Acknowledgments

This study was funded by the Dutch Organization for Scientific Research, NWO Grant 940-35-034 and Dutch Diabetes Research Foundation Grant DFN 98901.

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